
Molecular Mechanics Calculations of Conjugated Amides and an *Ab Initio* Investigation of Acrylamide and Its β -Amino Derivative: Conformational Analysis and Rotational Barriers

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ABSTRACT

Conformations and rotational barriers in a series of conjugated primary and tertiary amides have been analyzed by a modified MM2(91) force field, which treats the amide nitrogen as part of the conjugated system by redefining the atom type for the nitrogen. *Ab initio* molecular orbital calculations at the MP2/6-31G* level have been performed on the stable conformers and transition structures of acrylamide and β -*trans*-aminoacrylamide. The results have been used, with published experimental and computational data, to generate parameters for the MM2 force field. The force field has been applied to various conjugated amides, such as reduced nicotinamide adenine dinucleotide (NADH) and NAD⁺ analogues, nicotinamide, urea, vinylogous urea derivatives, and nucleic acid bases. The fundamental difference between primary and tertiary conjugated amides with respect to both conformation and barrier is highlighted. © 1996 by John Wiley & Sons, Inc.

Introduction

The NADH/NAD⁺ coenzyme is involved in many important biological oxidation reduction reactions. Details about the mechanism are not precisely known, but it has been suggested

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that the amide group in the enzyme complex is twisted out of the plane of the ring in the transition state of the reduction.¹ The migration of one of the two hydrides (*pro-S* or *pro-R*, Fig. 1) at the 4-position of the 1,4-dihydropyridine ring is favored, causing the hydride transfer to the substrate to be stereospecific. We are currently working on the stereodynamic properties of NADH/NAD⁺ analogues and have measured both the C—N barriers and, when possible, the C3—C7 barriers to rotation.² In this connection, it is

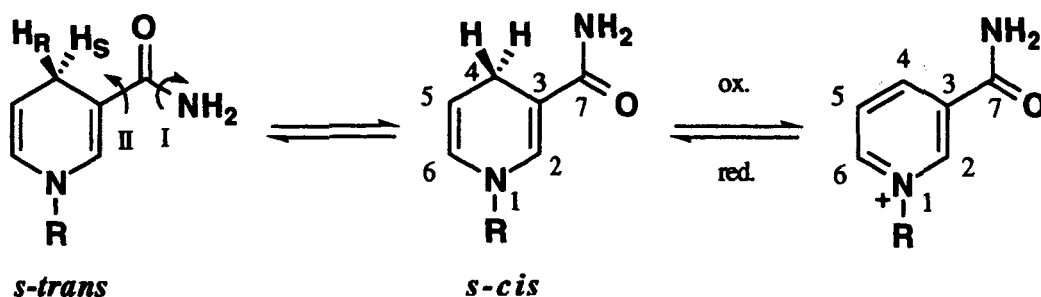


FIGURE 1. NADH and NAD⁺ analogues with the two examined amide rotations, the atom numbering, and the two conformers indicated.

of interest to perform modeling computations of NADH/NAD⁺ and related molecules. Accordingly, we wanted to perform calculations within a molecular mechanics framework. To accomplish such calculations, both C—C and C—N barriers must be acceptably reproduced. The amide group is not included in the π -system by the molecular mechanics program, and effects due to conjugation are consequently not adequately treated. Kontoyianni and Bowen have developed force field parameters for urea derivatives and some other conjugated amides.³ In their parameter database, they have compensated the lower barriers due to cross conjugation by lowering the torsional V_2 terms. This strategy, however, cannot handle extended π -systems with significantly different long-distance push or pull substituents. An example is *N,N*-dimethylacrylamide and its β -*trans*-*N,N*-dimethylamino derivative (2b and 5b in Fig. 3), which exhibit experimental rotational barriers of 16.7 and 12.4 kcal/mol, respectively.^{4,5} These values were determined in different solvents (chloroform and acetone) but certainly reflect the effect of long-distance conjugation. As is visualized in Figure 2, the different resonance structures in conjugated amides are highly affected by each other. The only possibility to reproduce this effect computationally is to include the amide nitrogen in the π -system. This work describes such an attempt. We have developed a force field parameter database pertaining to species that contain N—CO—N, C=C—CO—N and CO—N—C_{sp²} linkages within Allinger's force field MM2(91) by redefining the amide nitrogen as a π -atom.

A crucial reference compound is acrylamide, 2a, since it is the smallest conjugated system of this type, and we decided to examine it and its β -*trans*-amino derivative by *ab initio* calculations.

Methods

The *ab initio* calculations were performed on a Silicon Graphics IRIS workstation using the SPARTAN 3.0 program.⁶ The geometries were evaluated with full optimization at the restricted Hartree-Fock (RHF) level without symmetry restriction, employing the basis sets 3-21G and 6-31G* including MP2 electron correlation. Transition states were localized and vibrational frequencies were calculated for stable conformations and transition states verifying the existence of a single imaginary frequency in the latter cases. Default convergence criteria for self-consistent field (SCF) and geometry optimization were used.

The molecular mechanics calculations were performed using the MM2(91) force field implemented in the MacMimic program package.⁷ The torsional potentials were evaluated by driving the relevant torsion angles at 30° increments from 0 to 360°. All other bonds and angles were fully optimized. One more driver at 5° increments was performed around the transition state found in the first driver, to localize maxima separate from dihedral angles of 90°. The global minima were found by minimizing the lowest energy structure from the first driver without any restrictions.

In the original MM2 force field, the amide nitrogen is treated as an isolated unit with no provision for the influence of extended conjugation. However, the necessary SCF parameters are given in the program, and a simple redefinition of the amide nitrogen as a π -atom would lead to the desired influence on the torsional and stretching force constants in the molecular mechanics (MM) calculation. We have made use of that here and call the new atom type 9* to avoid ambiguity.

Torsional parameters (Table I) were developed

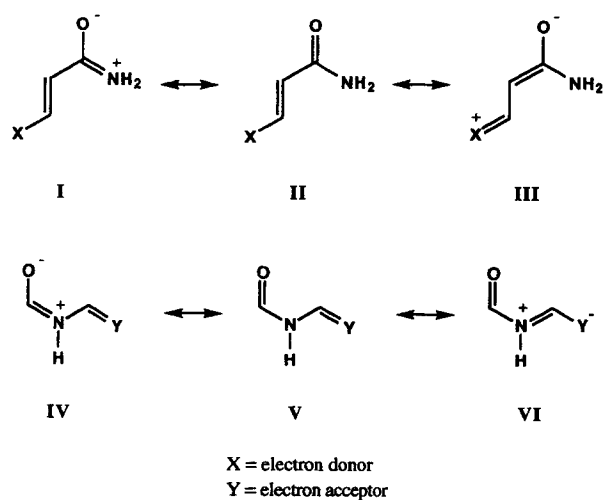


FIGURE 2. Resonance structures for the two possible kinds of conjugated amides.

so that the barriers to C—N rotation for structures 1–4 (Fig. 3) agreed with gas phase values (experimental or *ab initio*) or were extrapolated from experimental values in solution (Table II). Experimental gas phase data are available exclusively for 1b.⁸ The observed C—N barrier of 15.6 kcal/mol is ca. 2 kcal/mol higher than the calculated ΔG^\ddagger .⁹ We consider the experimental value, obtained by two independent groups, to be reliable and have used it in the parameterization and maintained the difference of 2 kcal/mol for the other molecules in the parameterization set. Only parameters missing and parameters involving atom type 9* were added to the parameter file. When possible, parameters for atom type 9 in the MM2(91) force field were transferred to atom type 9* in the parameter database. Torsional V_2 terms of type X—Y—9*—Z, where Y is an sp^2 -hybridized atom type, were roughly taken from the corresponding torsional V_2 terms of type X—Y—9—Z, corrected with the bond order times resonance integral value (P^*B) given for the Y—9* bond by the SCF calcu-

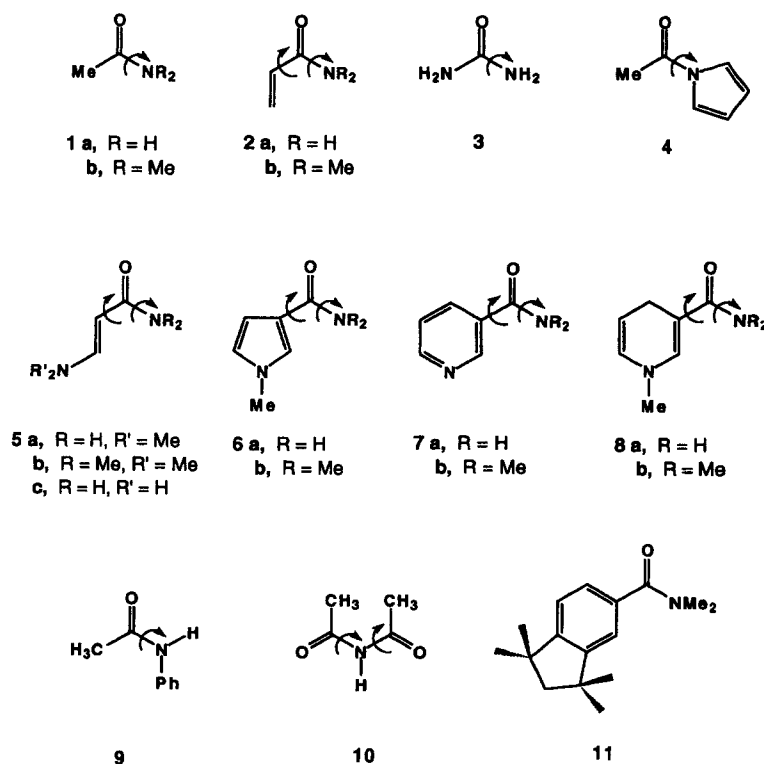


FIGURE 3. Chemical structures of the modeled amides (1–10). Arrows indicated the torsion angles examined for the generation of the corresponding rotational profiles. For all structures the *s-trans* conformer is shown.

TABLE I.
MM2(91) Force Field Parameters Valid for
Conjugated Amides with the Nitrogen Included
in the π System.^a

Atom Type				Torsional			
				V_1	V_2	V_3	
2	1	2	3	0.000	0.000	0.600	
1	2	2	9	0.000	15.000	0.000	
2	2	9	1	1.850	7.200	0.000	
1	3	9	1	1.100	7.720	0.000	
1	2	3	9	1.000	7.500	0.000	
1	3	9	2	-4.000	7.400	0.500	
2	3	9	1	0.000	8.450	0.000	
2	2	3	9	3.400	7.500	0.000	
2	2	9	3	0.000	1.500	0.000	
3	2	2	9	0.000	15.000	0.000	
1	3	9	3	-0.900	6.000	0.000	
5	2	9	1	1.850	7.200	0.000	
5	2	9	2	0.000	15.000	0.000	
5	2	3	9	0.700	2.200	0.000	
5	2	9	3	0.000	1.500	0.000	
7	3	9	1	0.000	7.720	0.000	
7	3	9	2	-3.100	8.050	0.000	
7	3	9	3	0.000	6.000	0.000	
1	3	9	28	0.000	5.950	0.000	
2	3	9	28	0.000	5.600	0.000	
7	3	9	28	1.100	5.950	0.000	
9	3	9	28	0.000	3.900	0.000	
3	2	2	37	0.000	15.000	0.000	
2	2	40	1	1.850	7.200	0.000	
3	2	2	40	0.000	15.000	0.000	
5	1	40	2	0.000	0.000	0.000	
5	2	40	1	1.850	7.200	0.000	
				Stretching			
				k_S	l_0	slps	slpt
3	9			6.400	1.320	2.000	0.100
1	40			3.520	1.437		
				Bending			
				k_B	θ		
2	3	9		0.500	120.0		
1	40	2		0.630	119.9		
5	1	40		0.420	109.0		
0	9	1		0.800			
0	9	2		0.800			
0	9	3		0.800			
0	9	28		0.800			
0	3	9		0.100			
0	40	1		0.050			

^aUnits: Stretching constants in md/Å, bond lengths in Å, bending constants in mdÅ/rad², and angles in degrees.

lation. That is,

$$V_2(X-Y-9^*-Z) \\ = V_2(X-Y-9-Z)/P * B(Y-9^*)$$

The parameter database was tested by calculating the barriers to C—N rotation for structures 5–10 (Fig. 3) and comparing them with experimental values (Table II).

Results and Discussion

Acrylamide, **2a**, is a key molecule since it is the parent compound among conjugated amides. No experimental values for the rotational barriers have been reported for **2a**, and we therefore performed an *ab initio* analysis, including full geometry optimization and transition state localization, on the 3-21G and MP2/6-31G* levels that also included an analysis of the β -trans-amino derivative, **5c**. Some results are shown in Table III and Figure 4. Two conformers were found, *s-cis* and *s-trans*, with *s-cis* being the only significantly populated ($\Delta E^\circ = 2.68$ and 4.76 kcal/mol, respectively for **2a** and **5c**). The *s-cis* conformer is planar, whereas *s-trans* is twisted 25°/18° (for **2a** and **5c**, respectively) around the C2—C3 bond and has a slightly pyramidalized nitrogen (N 0.19/0.25 Å from the H—H—C plane). In the transition state for the C—N rotation, the nitrogen is pyramidal (N 0.42 Å from the H—H—C plane) with the lone pair anti to the carbonyl bond. A similar preference for the anti form over the syn form was calculated for *N,N*-dimethylacetamide.⁹ The transition state for the C—C rotation had a C=C—C=O dihedral angle of 86/89°. Rotational barriers at 298 K, ΔE^\ddagger , were calculated for both C—C and C—N rotations, obtained from the sum of the changes in the electronic energy the zero point vibrational energy, ΔE_{ZPE} and the thermal correction to the zero point energy. The C—N barriers at the MP2/6-31G* level for **2a** and **5c**, 14.61 and 13.17 kcal/mol, can be compared with similar computations on acetamide,¹⁰ $\Delta E^\ddagger = 14.35$ kcal/mol (6-31G*), and *N,N*-dimethylacetamide,⁹ $\Delta E^\ddagger = 13.4$ kcal/mol (6-31G*).

The *ab initio* calculations show that the H—N—H bond angle in both primary and tertiary amides gets distorted on rotation about the C—N bond.^{9,10} This is indicative of pyramidalization about the nitrogen. Kontoyianni and Bowen³ stated that "the changes in hybridization of the nitrogen atom as a function of the rotation about the C—N

TABLE II.
Calculated (ΔE) and Experimental (ΔH and ΔG) Barriers to Rotation and Relative Conformer Energies for Structures 1–10 with Amide Nitrogen of Type 9*.

Compound ^a		MM2(91)		Reference Values			
		$\Delta E^{\ddagger b}$	$\Delta E^{\circ c}$	ΔH^{\ddagger}	ΔG^{\ddagger}	ΔE^{\ddagger}	ΔE°
1a	(O=C—N—H)	16.2	—	18.2 ^f	16.7 ^f	14.2 ^g	
1b	(O=C—N—C _{sp} ³)	15.5	—	15.8 ^h	15.6 ^h	13.6 ⁱ	
2a	(O=C—N—H) ^d	15.8	—			14.6 ^j	
	(O=C—C=C)	5.2	2.7			4.8 ^j	2.7 ^j
2b	(O=C—N—C _{sp} ³)	15.0	—	16.2 ^k	16.7 ^k		
	(O=C—C=C)	8.7	^e				
3	(O=C—N—H)	11.5	—		11.4 ^l	8.0 ^m	
4	(O=C—N—C _{sp} ²)	12.5	—	12.7 ⁿ		12.6 ^o	
5a	(O=C—N—H) ^d	15.6	—			13.2 ^j	
	(O=C—C=C)	6.0	3.0			8.7 ^j	4.8 ^j
5b	(O=C—N—C _{sp} ³)	14.8	—		12.4 ^p		
	(O=C—C=C)	9.1	^e				
6a	(O=C—N—H) ^d	16.6	—				
	(O=C—C=C)	4.3	0.1				
6b	(O=C—N—C _{sp} ³)	12.9	—		14.6 ^q		
	(O=C—C=C)	1.7	^e				
7a	(O=C—N—H) ^d	16.4	—		13.0 ^r		
	(O=C—C=C)	3.3	0.1				
7b	(O=C—N—C _{sp} ³)	13.8	—		15.8 ^s / 14.9 ^r		
	(O=C—C=C)	5.9	^e				
8a	(O=C—N—H) ^d	15.6	—		11.4 ^t		
	(O=C—C=C)	6.3	1.9			7.0 ^u	1.0 ^u
8b	(O=C—N—C _{sp} ³)	11.0	—				
	(O=C—C=C)	0.9	^e				
9	(O=C—N—C _{sp} ²)	13.0	1.9			11.9 ^v	2.1 ^v
10	(O=C—N—C _{sp} ³)				10.8 ^x		
	(ZE → ZZ)	12.1	−2.9			11.4 ^v	6.5 ^v
	(EE → EZ)	10.2	−0.2				

All energies in kcal / mol.

^aThe atoms defining the torsional angle are shown in parentheses.

^bMajor to minor conformer.

^c $E^{\circ}(s\text{-trans}) - E^{\circ}(s\text{-cis})$.

^dThe barrier is calculated for the *s-cis* conformer.

^eSteric barrier over the planar state.

^fAcetone (ref. 18).

^g*Ab initio* MP2 / 6-31G* (ref. 10).

^hGas phase (ref. 8).

ⁱ*Ab initio* 6-31G* (ref. 9).

^j*Ab initio* MP2 / 6-31G*, this work
 (values for **5a** represented by those for **5c**).

^kChloroform (ref. 4).

^lAcetone and TMU (ref. 18).

^m*Ab initio* 6-31G* (ref. 3).

ⁿChloroform-*d* (ref. 19).

^o*Ab initio* 6-31G** (ref. 15).

^pAcetone-*d*₆ (ref. 5).

^q*N,N*-dimethyl-3-pyrrolamide in chloroform-*d* (ref. 20).

^rToluene-*d*₈ (ref. 2).

^sChloroform-*d* (refs. 2 and 21).

^t1-Benzyl-1,4-dihydronicotinamide in chloroform-*d* (ref. 2).

^u*Ab initio* 6-31G* (ref. 16a).

^v*Ab initio* 6-31G* (ref. 3).

^xAcetone, ZE → EZ (ref. 14).

bond cannot be reproduced by MM2." This is indeed true. The atom types in MM2 have fixed hybridizations, which do not change when the conformation is changed. Kontoyianni and Bowen chose, when creating their MM2 force field parameters for urea, to reproduce the C—N rotational barrier given by *ab initio* calculations with the amide nitrogen constrained to be planar. Our in-

tention was to reproduce the "real" barrier to rotation and accept that the amide nitrogen, in the MM2 calculations, will assume a planar transition geometry.[†] Thus, the parameters for the torsional

[†]The barrier to C—N rotation in urea presented by Kontoyianni and Bowen is 17.7 (*ab initio*) or 17.9 [MM2(87)] kcal/mol, to be compared with the experimental and our value presented in Table II.

TABLE III.
Energy Data for Stable Conformations and Transition States of Acrylamide, 2a, and Its β -trans-Amino Derivative, 5c, Calculated by Various *Ab Initio* Basis Sets.

2a	3-21G ^a	6-31G ^{*a}	MP2/6-31G ^{*a}	ZPE ^b	E _{th} ^c
<i>s-cis</i>	-244.450268	-245.820069	-246.528403	47.41	48.33
<i>s-trans</i>	-244.444733	-245.817587	-246.526266	47.89	49.19
C—C TS	-244.437883	-245.811501	-246.520845	47.38	48.42
C—N TS ^c	-244.423115	-245.797531	-246.505341	47.40	48.49
ΔE ^o (<i>s-trans-s-cis</i>)	3.47	1.56	1.34		
ΔE [‡] (C—C) ^d	7.77	5.38	4.74		
ΔE [‡] (C—N) ^e	17.04	14.14	14.47		
ΣΔE ^o (<i>s-trans-s-cis</i>) ^f		2.75	2.53		
ΣΔE [‡] (C—C) ^f		5.43	4.79		
ΣΔE [‡] (C—N) ^f		14.28	14.61		

5c	6-31G ^{*a}	MP2/6-31G ^{*a}	ZPE ^b	E _{th} ^c
<i>s-cis</i>	-300.857215	-301.727191	57.17	59.04
<i>s-trans</i>	-300.852265	-301.724373	58.65	60.55
C—C TS	-300.842802	-301.715495	57.87	59.69
C—N TS ^c	-300.837228	-301.708564	57.96	59.73
ΔE ^o (<i>s-trans-s-cis</i>)	3.10	1.77		
ΔE [‡] (C—C) ^d	9.04	7.34		
ΔE [‡] (C—N) ^e	12.54	11.69		
ΣΔE ^o (<i>s-trans-s-cis</i>) ^f		3.28		
ΣΔE [‡] (C—C) ^f		8.69		
ΣΔE [‡] (C—N) ^f		13.17		

^aTotal energies in hartrees.

^bZero point energy (6-31G^{*}) in kcal/mol, scaled by the factor 0.89.²²

^cThermal vibrational energy in kcal/mol at 298 K.

^dRelative the *s-cis* conformer.

^eIn the *s-cis* conformation.

^fAfter correction for zero point energy and thermal vibration at 298 K.

angles O=C—N—H and O=C—N—C were derived to generate the experimental gas phase barriers to C—N rotation for structures 1–4, even though the transition structures are not reproduced. The relative conformer energies and rotational barriers in structures 1–10 are summarized in Table II.

MINIMAL ENERGY CONFORMATION

All primary amides are calculated to be planar in the minimal energy conformation and prefer the *s-cis* conformation (as defined in Fig. 1). The relative populations of *s-cis* and *s-trans* conformers are in most cases unknown. The minimal energy conformation energy data obtained in the *ab initio* calculations for acrylamide, summarized in Table III, are the basis of some of the more important torsional parameters in our parameter database. However, the V_1 terms are further established by the infrared (IR) spectrum of acrylamide, suggest-

ing that the *s-cis* orientation is strongly favored in the gas phase,¹¹ and the findings that NADH analogues are predominantly *s-cis*.¹² The energy differences between the *s-cis* and *s-trans* conformers have not been experimentally established in these cases, but dynamic nuclear magnetic resonance (NMR) studies in various solvents indicate that $\Delta G^\circ \geq 2.0$ kcal/mol.² The energy difference between *s-cis* and *s-trans* conformers is predicted by our calculations to be minute in both heteroaromatics 6a and 7a.

Among the tertiary amides, the heterocyclic compounds, 6b, 7b, and 8b, are twisted in the minimal energy conformation; while the open chain structures, 2b and 5b, are *s-cis* planar, according to these calculations.

C—N AND C—C BARRIERS

The magnitude of the C—N rotational barrier depends on the extent and character of the cross

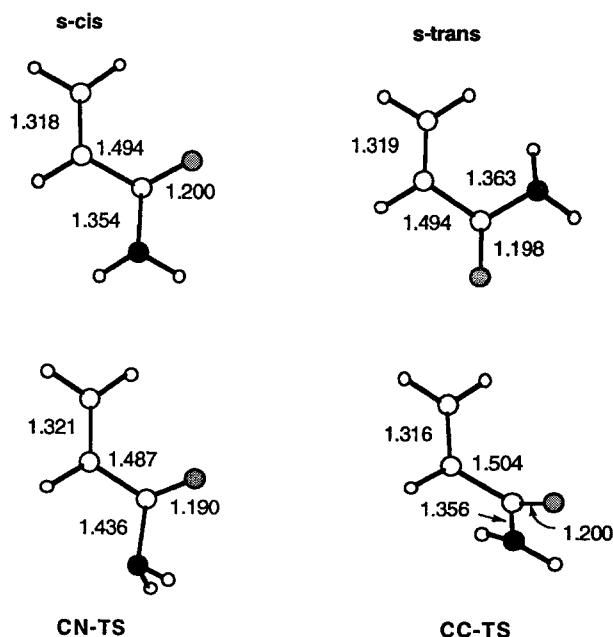


FIGURE 4. Selected bond lengths for the *s-cis* and *s-trans* initial states and for the C—N and C—C transition states of acrylamide calculated at the MP2 / 6-31G* level.

conjugation shown in Figure 2. If the cross conjugation is directed to the amide carbonyl (canonical form III in Fig. 2), the double bond character of the C—N bond is lowered, and so is the C—N rotational barrier. This is reflected by the more important contribution of resonance structure III when X is an electron donor. The same argument also suggests a higher C—C barrier, which is indeed observed. If the cross conjugation is headed from the amide nitrogen (canonical form VI in Fig. 2), as is the case when Y is an electron acceptor, the double bond character of the C—N bond and the rotational barrier is lowered. The second case is represented in structures 4, 9, and 10. The magnitude of the various effects is determined by the efficiency of the donor/acceptor groups and is manifested in the bond order in the SCF calculations.

In all investigated structures, the calculated barrier to C—N rotation is much higher than the barrier to C—C rotation. Figure 5 shows the torsional potential energy profiles for some selected structures. The ability of the force field to accommodate cross conjugation on the C—N and C—C barriers in primary amides is seen in 2a, 5a, 6a, 7a, and 8a. The C—N barrier in 5a is slightly smaller than in 2a, whereas an opposite and stronger effect was found for the C—C barrier. These effects are then modulated in the other systems, 6a, 7a, and

8a, according to their respective electron donating or accepting ability. Hence the calculated barrier to C3—C7 rotation in structure 7a is lower than the corresponding barrier in structures 5a and 8a. On the other hand, the barrier to C—N rotation is slightly higher in structure 7a. This is what could be expected since the pyridine ring is electron attracting, while the vinylogous amide nitrogen and the 1,4-dihydropyridine nitrogen are electron donating and exert the opposite effect. The effects are qualitatively reproduced with this parameter data set, although the variation in C—N barriers tends to be underestimated. The effects of including the amide nitrogen in the SCF calculations compared to the standard MM2(91) force field² can be seen for the acrylamides, 2, and the nicotinic amides, 7, in Table IV.

The tertiary amides, on the other hand, have steric C—C rotational barriers over planar transition states. Structures 2b and 5b are planar both in the initial and transition states (*s-cis* and *s-trans*, respectively). The different C—C barrier for structures 6b and 7b reflects the larger steric demand of the pyridine ring compared to the smaller pyrrole ring. Structure 8b, on the other hand, is affected by both electronic and steric differences.

Experimental values for the barrier to C—C rotation in this type of system are scarce in the literature. We have recently estimated the C—C barrier in the benzamide analogue 11 in (CD₃)₂O solution as 5.8 ± 0.5 kcal/mol², in excellent agreement with the calculated value 5.9 kcal/mol for 7b, also after consideration of solvent effects and the different electron releasing abilities of the benzene and pyridine rings. Experimental values for the C—N rotational barriers in tertiary amides are much more abundant.¹³ They are acceptably reproduced with our force field parameters, even though the large solvent effects must be taken into account (Table II). Often, only ΔG^\ddagger values have been measured. This makes the gas phase experiments on dimethylacetamide of great value.⁸ Due to the hydrogen bonding capability of primary amides, solvent effects become too dominating for comparisons between experimental ΔH^\ddagger and calculated ΔE^\ddagger values to be meaningful.

Figure 6 shows the torsional potential energy profiles for 9 and 10. Kontoyianni and Bowen made *ab initio* calculations on these structures and

²Some parameters had to be added: 2-3-9-28: $V_1 = 0$, $V_2 = 3.4$, $V_3 = 0$ (taken from 2-3-9-28 in Table I, but with the V_2 term corrected with P^*B); 3-2-2-37: $V_1 = 0$, $V_2 = 15.0$, $V_3 = 0$; 5-2-3-9: $V_1 = 0$, $V_2 = 7.5$, $V_3 = 0$; 0-9-1, 0-9-3, 0-9-28: $k_B = 0.8$ (all given the same values as in our parameter database).

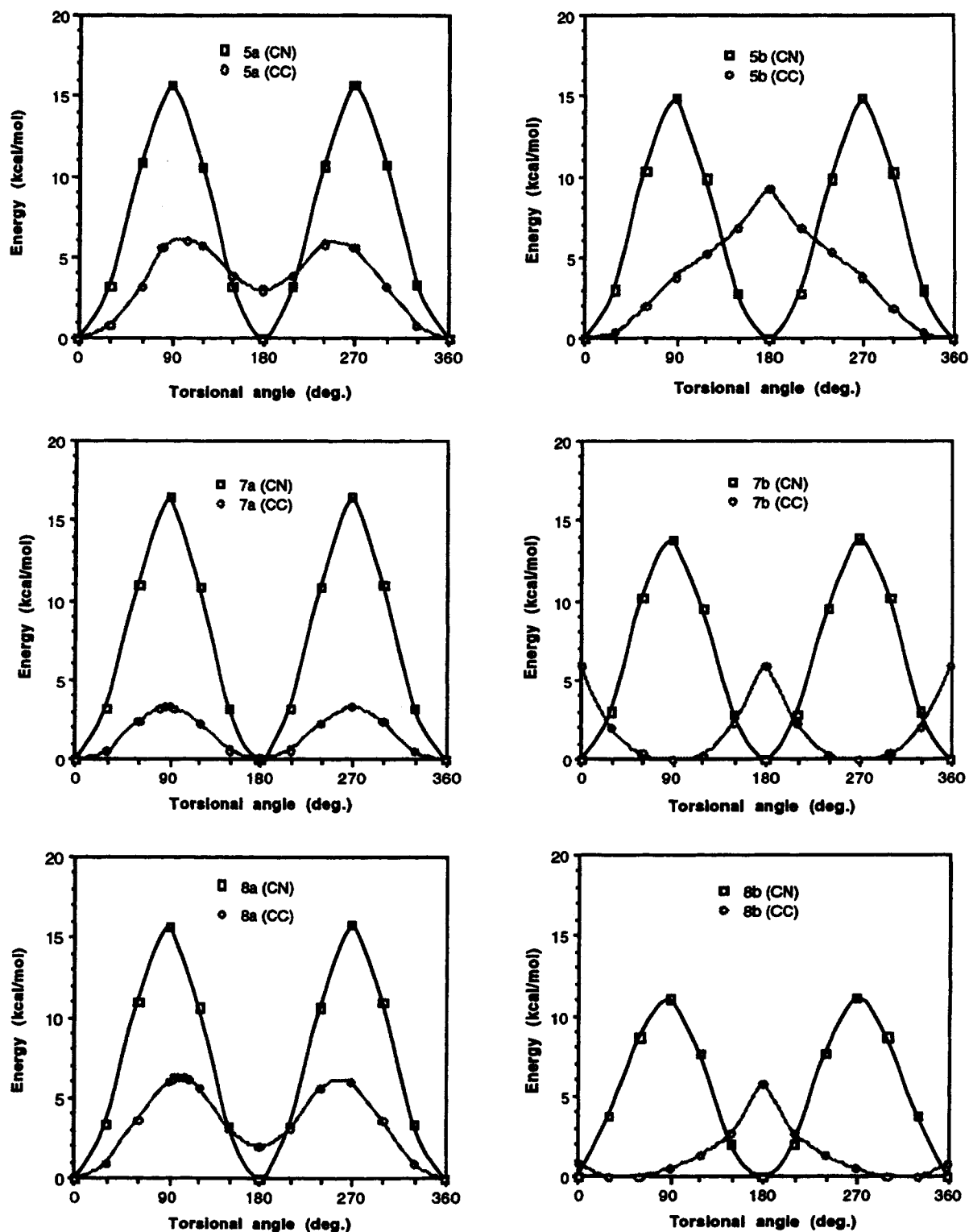


FIGURE 5. MM2(91) relative potential energy profiles as a function of rotation about the $\text{O}=\text{C}-\text{N}-\text{H}$, $\text{O}=\text{C}-\text{N}-\text{Me}$, and $\text{O}=\text{C}-\text{C}=\text{C}$ bonds in some selected vinylogous urea derivatives with amide nitrogen type 9*.

TABLE IV.
Calculated Barriers to Rotation and Relative Conformer Energies of Structures 2 and 7 with Amide Nitrogen of Type 9* and 9.

Nitrogen Type Compound ^c	9* ^a		9 ^b	
	$\Delta E^{\ddagger d}$	ΔE^{oe}	$\Delta E^{\ddagger d}$	ΔE^{oe}
2a (O=C—N—H)	15.8	—	19.6	—
(O=C—C=C)	5.2	2.7	3.4	-0.8
2b (O=C—N—C _{sp} ³)	15.0	—	17.2	—
(O=C—C=C)	8.7	—	8.2	—
7a (O=C—N—H)	16.4	—	20.0	—
(O=C—C=C)	3.3	0.1	1.9	0.1
7b (O=C—N—C _{sp} ³)	13.8	—	17.4	—
(O=C—C=C)	5.9	—	9.3	—

All energies in kcal/mol.

^aData from Table II.

^bSee note ‡ in text.

^cThe atoms defining the torsional angle is shown in parentheses.

^dMajor to minor conformer.

^e $E^o(s-trans) - E^o(s-cis)$.

used the result for molecular mechanics parameterization. Their results are included in Figure 6. The potential energy profile for 9 agrees well with the *ab initio* results. The authors have chosen not to assign a high force constant to the N—C_{sp}² out-of-plane bending and have, consequently, a pyramidal transition geometry. This explains the somewhat deformed shape of the energy profile with their MM2(87) calculated results. When trying to reproduce the *ab initio* results for structure 10, we faced some unexpected problems. The

height of the rotational barrier is reproduced, but we failed to reproduce the energy differences between the three possible conformers. It is known that the *EZ* conformer is dominating.¹⁴ In particular, the *ZZ* conformation is unjustifiably favored in our calculations, but to some extent also *EE*. The reason for this could be traced to the way the program handles the bond dipole contribution to the steric energy. When the molecule is classified as a conjugated system, bond dipole constants (e.g., for the C=O bond) are automatically changed for bonds isolated from the conjugated π -system, leading to incorrect dipole energy contributions to the steric energy.⁸

Compound 4 represents an interesting example since the nitrogen atom is defined as both atom types 9 and 40 in MM2. We used atom type 9* and used standard atom type 40 parameters when available. The low barrier illustrates the effects of cross conjugation over the nitrogen atom.¹⁵

Wu and Houk¹⁶ recently reported *ab initio* (6-31G* basis set) results on 1,4-dihydronicotinamide and calculated a preference of 1.0 kcal/mol for the *s-cis* conformer and a C—C barrier of 7.0 kcal/mol, compared with our values 1.9 and 6.3 kcal/mol, respectively, for the *N*-methyl derivative 8a.

⁸This change in bond dipole moment has been introduced to generate correct molecular dipole moments, when added to the π -moments generated by the SCF calculation. There is no reason to maintain this change in the dipole term of the steric energy calculation, and it should be considered as an artifact in the MM2 program. This artifact does not appear in MM3.

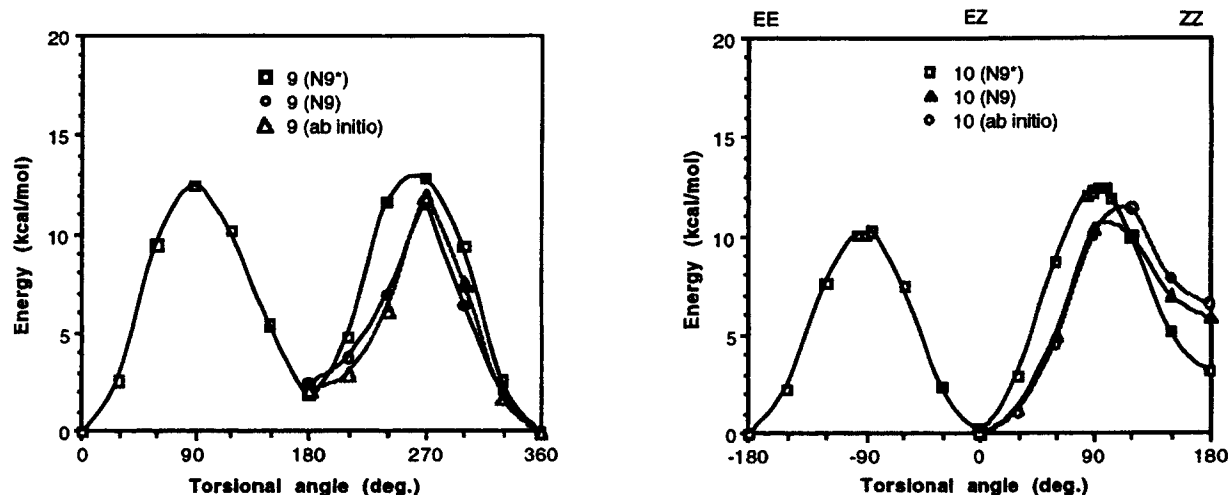


FIGURE 6. Relative potential energy as a function of rotation about the O=C—N—Ph bond in acetanilide (9) and the C—N bonds in *N*-acetylacetamide (10). The conformations for structure 10 are indicated along the upper edge (the values on the abscissa refer to different dihedral angles).

GEOMETRIES

Selected structural features for amides 1–10 predicted by MM2(91) calculations are presented in Table V. Good agreement with *ab initio* results for 2a is obtained, and the trends in bond length variation on rotation were reproduced. The $C_{\text{carb}}-\text{N}$ bonds are longer for the tertiary than the primary amides both in the minimum energy and transition structures, due to steric interactions. The $C_{\text{carb}}-\text{N}$ bond is about 0.04 Å longer when rotated 90°, due to loss of π -character of the bond, in agreement with *ab initio* results.^{9,16} At the same time, the $C_{\text{sp}^2}-C_{\text{carb}}$ bond in most of the systems, 2 and 5–8, is shortened by 0.01–0.04 Å when the $C_{\text{carb}}-\text{N}$ bond is rotated, due to both decreased steric demands in the molecule and increased double bond character of the $C_{\text{sp}^2}-C_{\text{carb}}$ bond. The former contribution is probably dominating, since no effects are seen on structures 2a and 7a. On the other hand, when the $C_{\text{sp}^2}-C_{\text{carb}}$ bond is rotated to the transition geometry, the $C_{\text{carb}}-\text{N}$ bond length is generally not affected. The $C_{\text{sp}^2}-C_{\text{carb}}$ bond itself gets 0.03 Å longer in the primary amides when rotated out of the plane. The transition geometry for the tertiary amides is planar over the $C_{\text{sp}^2}-C_{\text{carb}}$ bond since the barriers are steric. Here the bond is lengthened by 0.01 Å for structures 2b and 5b, when changing from the planar initial state to the planar transition state. For structures 6b and 7b, the bond is shortened by 0.01–0.02 Å, and for structure 8b it is unaffected compared to the same bond in the twisted initial state. The bond lengthening for structures 2b and 5b can be explained by steric effects only. The bond shortening in structures 6b and 7b can, on the other hand, only be explained by gain in resonance energy, since the bond is rotated from a twisted, less crowded initial state geometry to a planar more crowded transition state, which normally would lead to bond lengthening to avoid steric interactions.

As far as bond angles are concerned, the $C_{\text{carb}}-\text{N}-\text{H}$ and $C_{\text{carb}}-\text{N}-\text{C}$ angles in the minimized structures are always smaller when directed cis than when directed trans to the carbonyl oxygen (see structures 1–8). This has been observed in *ab initio* calculations for formamide and has been explained by a hydrogen bond between the amide proton and carbonyl oxygen.³ This cannot be the only explanation, since the same trend is observed for tertiary amides with different substituents not able to form hydrogen bonds. The $C_{\text{carb}}-\text{N}-\text{H}$ angles are smaller than the $C_{\text{carb}}-\text{N}-\text{C}$ angles.

The dihedral $\text{O}=\text{C}-\text{C}=\text{C}$ angles for the structures twisted in the initial state, 6b, 7b, and 8b, are 126, 91, and 38°, respectively. The transition states for the $\text{C}-\text{C}$ rotation in the primary vinylic systems have dihedral $\text{O}=\text{C}-\text{C}=\text{C}$ angles of 105° for structures 2a, 5a, and 8a, 85° for structures 6a and 7a. The corresponding *ab initio* value is 86° in both 2a and 8a.^{16a}

The fundamental difference between primary and tertiary amides emerges from the data in Table II and is shown in Figure 5. Primary amides are essentially planar molecules with $\pi-\text{C}-\text{C}$ barriers in the range of 3–6 kcal/mol over twisted transition states, whereas tertiary amides are twisted in the initial state with steric barriers over the planar transition state. This may have implications on model studies of NADH reduction, in the transition state of which a twisted amide has been postulated.¹

The effect of cross conjugation in the studied compounds is handled qualitatively correctly by this approach, but it tends to be slightly underestimated, particularly for the $\text{C}-\text{N}$ barrier. The reason for this is the small variation in the V_2 -modulating factor $P * B$. A closer comparison with experimental barriers is hampered by the important solvent effects, but the agreement is in general good. In a few cases, calculated $\text{C}-\text{N}$ barriers are higher than reported experimental data for primary amides (e.g., 8a), indicating possible competing proton exchange mechanism.

Finally, the proposed force field modification is easily extended to other interesting systems, such as nucleic acid bases. Two examples are shown in Figure 7 (adenine and thymine) and are compared to recent *ab initio* calculations by Stewart et al.¹⁷ In adenine, two nitrogen atoms are defined as atom type 9* and three as pyridine nitrogen type 37. In thymine, there are two atom type 9* nitrogens. All heavy atoms (except methyl carbon) are included in the SCF calculation. On the whole, the MM2 values are in good agreement with the *ab initio* results. We plan to extend and refine this force field for the entire set of nucleic acid bases.

Conclusions

An *ab initio* study of acrylamide and β -trans-aminoacrylamide, including transition state localization and characterization at various levels, has been performed showing that the *s-cis* conformation is planar and ca. 2.6–4.8 kcal/mol more stable

TABLE V.
MM2(91) Values for Selected Structural Features for the Ground State Geometries.^a

Features	1a	1b	2a	2b	3	4	5a	5b	6a	6b	7a	7b	8a	8b	9	10
Bond lengths																
C _{carb} —N	1.36	1.38	1.35	1.39	1.36	1.38	1.36	1.39	1.35	1.38	1.35	1.38	1.36	1.38	1.37	1.38
C _{carb} —C	1.52	1.52	1.48	1.49		1.52	1.48	1.48	1.48	1.50	1.48	1.52	1.48	1.50	1.52	1.52
C _{carb} =O	1.22	1.22	1.22	1.23	1.23	1.22	1.23	1.23	1.22	1.22	1.22	1.22	1.23	1.23	1.22	1.22
N—C _{sp²}						1.35									1.35	
Bond angles																
O=C—N	119.8	122.3	118.7	120.4	119.5	122.5	118.7	120.3	119.4	121.8	117.9	122.7	117.9	119.5	125.6	117.9
N—C _{carb} —N					120.9											124.4
C—C _{carb} —N	117.0	119.4	117.6	121.7		118.5	117.7	121.9	118.0	122.0	119.4	120.1	118.4	125.0	114.5	120.3
C _{carb} —N—H ^b	115.5		115.6		115.2		115.6		116.0		115.6		115.4			115.0
C _{carb} —N—H ^c	120.4		119.6		120.4		119.6		119.0		119.6		119.9		121.7	117.1
C _{carb} —N—C ^b		117.0		117.1		125.3		117.1		117.2		117.5		116.8	126.7	131.3
C _{carb} —N—C ^c		120.1		120.2		128.3		120.3		120.1		119.1		121.1		
Torsion angles																
O=C—N—H ^b	0.0		0.0		0.0		0.0		0.0		0.0		0.0			0.0
O=C—N—H ^c	180.0		180.0		180.0		180.0		180.0		180.0		180.0		—174.2	180.0
O=C—N—C ^b		0.0		—0.1		0.0		0.0		—3.1		0.2		—4.0	1.9	0.0
O=C—N—C ^c		180.0		179.9		180.0		180.0		175.5		—179.7		174.0		180.0
O=C—C=C			0.0	0.1			0.0	0.1	0.0	126.4	0.1	—91.2	0.0	—37.6		
C _{carb} —N—C=C															21.5	

Transition Geometries for C—N Rotation

Bond lengths																
C _{carb} —N	1.40	1.42	1.41	1.42	1.41	1.41	1.41	1.42	1.40	1.42	1.40	1.42	1.41	1.42	1.39	1.41
C _{carb} —C	1.52	1.52	1.48	1.48		1.52	1.47	1.47	1.47	1.47	1.48	1.48	1.47	1.48	1.52	1.52
C _{carb} =O	1.21	1.21	1.21	1.21	1.22	1.21	1.22	1.22	1.21	1.22	1.21	1.22	1.22	1.22	1.21	1.22
N—C _{sp²}						1.35									1.35	1.21
Bond angles																
O=C—N	121.4	122.5	120.3	121.2	121.5	122.6	120.2	121.1	120.6	121.4	119.6	120.2	119.6	120.1	122.5	118.9
N—C _{carb} —N					119.2											122.0
C—C _{carb} —N	116.2	116.0	116.9	117.0	119.4	115.9	117.1	117.2	117.8	118.6	118.4	119.4	117.5	118.5	115.7	118.5

$C_{carb}-N-H$	118.4	118.3	118.2	118.3	118.2	118.3	123.7	115.9
$C_{carb}-N-H$	118.5	118.3	118.3	118.4	118.3	118.3		113.8
$C_{carb}-N-C$	117.3	117.5	117.5	117.5	117.5	117.6	117.6	118.2
$C_{carb}-N-C$	117.7	117.5	117.5	117.5	117.6	117.6	123.0	128.0
Torsion angles								
$O=C-N-H$	-86.4	-89.1	-87.6	-89.9	-93.8	-89.5	-109.7	1.0
$O=C-N-H$	90.0	90.0	90.0	90.0	89.9	90.0		-98.2
$O=C-N-C$	-85.1	-88.6	-90.2	-96.0	-88.8	-87.6	-85.4	85.0
$O=C-N-C$	90.0	90.0	90.0	90.0	90.0	90.0	90.0	178.0
$O=C-C=C$	0.5	0.7	0.5	-0.2	-3.4	-179.7	-1.1	-1.5
$C_{carb}-N-C=C$							-6.5	

Transition Geometries for C—C Rotation

Bond lengths								
$C_{carb}-N$	1.35	1.39	1.35	1.35	1.39	1.35	1.39	1.39
$C_{carb}-C$	1.51	1.50	1.51	1.49	1.51	1.50	1.51	1.50
$C_{carb}=O$	1.22	1.23	1.23	1.22	1.23	1.23	1.22	1.23
Bond angles								
$O=C-N$	120.1	118.6	120.2	118.3	120.3	118.8	120.3	117.0
$C-C_{carb}-N$	117.5	129.4	117.4	129.8	117.1	127.5	117.2	127.4
$C_{carb}-N-H^b$	116.0		116.0		116.0		116.1	
$C_{carb}-N-H^c$	119.1		119.2		119.1		119.0	
$C_{carb}-N-C^b$	116.2		116.1		116.5		116.1	116.2
$C_{carb}-N-C^c$	122.3		122.6		121.9		123.1	122.7
Torsion angles								
$O=C-N-H^b$	-0.2		0.0		-0.4		-0.5	0.7
$O=C-N-H^c$	180.0		-179.8		179.5		179.5	-179.0
$O=C-N-C^b$	-0.7		-1.0		-0.4		0.4	-0.8
$O=C-N-C^c$	179.2		178.8		179.5		-179.5	179.0
$O=C-C=C$	105.0		105.0		85.0		85.0	105.0
					180.0		0.0	0.0

^aBond lengths in Å and angles in degrees.^bCis to the carbonyl oxygen.^cTrans to the carbonyl oxygen.

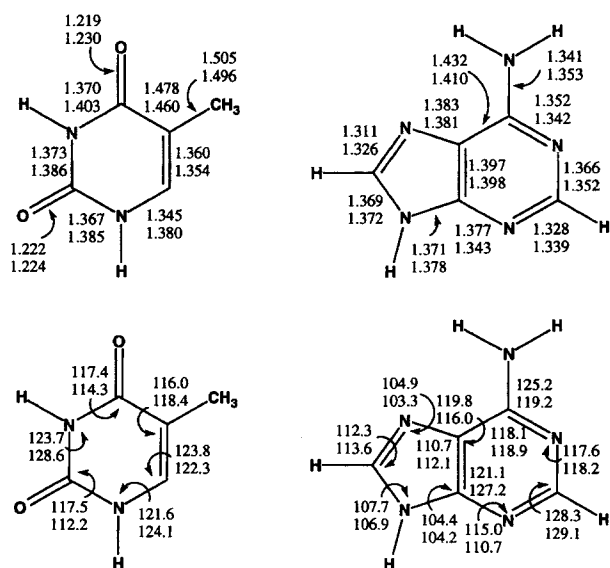


FIGURE 7. Selected structural parameters for thymine and adenine calculated by our MM2 force field (upper values) and MP2/6-31G**.

than *s-trans*, which is twisted ca. 25° due to steric interactions. The MM2(91) force field has been extended to include the amide nitrogen into the π -system. Experimental and *ab initio* gas phase geometries and rotational barriers of several conjugated amide derivatives are usually well reproduced. We consider this approach basically sound, since both barriers and bond lengths are modulated by bond order and resonance integral. Several biologically important systems, such as NADH/NAD⁺, nicotinamide, urea, and two nucleic acid bases, have been examined and show good agreement with experimental and *ab initio* results.

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